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MEDICAL PROGRESS

Hirsutism and Virilization

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■ *In normal females, androstenedione from both the adrenal cortex and ovary, as a result of peripheral conversion, is the source of the majority of biologically active testosterone in the circulation. The control of the secretion of precursor steroid and androgenic hormone (testosterone) in females is not clear at this time. There are a number of possibilities to explain various types of hirsutism and virilization. The presence of true virilization indicates a significant disorder and requires complete investigation.*

The presence of increased amounts of 17-ketosteroids in the urine implicates the adrenal cortex as a source of the pathologic manifestations. The suppressibility of elevated 17-ketosteroids with cortisol analogues aids in distinguishing between adrenal hyperplasia and autonomous neoplasm of the adrenal cortex.

By far the most common entity in this area is simple hirsutism without virilization. Although our knowledge of this disorder is quite incomplete, conservative management is indicated. Further progress in this field is rapidly occurring. An informed clinician can do an adequate job of diagnosis and treatment with the clinical and laboratory tools generally available.

TREMENDOUS advances in our knowledge of adrenal cortical and gonadal physiology and pathology have occurred in the last 25 years. Although many aspects of this field have been extensively investigated, the limitations of methodology have only recently allowed progress in our understanding of androgen metabolism. This review will of necessity deal with current concepts of physiology and classification. Since the knowledge in this field is so new and changing, this paper must be considered more a progress report, than an elucidation of fixed truths.

Androgens are substances which cause the development of the primary and secondary sexual tissues of the male and analogous structures in the female. Androgens have general anabolic effects upon muscle, skin and its appendages, fat distribution, behavior, and growth rate. These hormones

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interact on DNA-RNA exchange of information at the nuclear level and thereby influence protein synthesis.

Of the known androgenic substances, only testosterone, a C-19 steroid, and to a much lesser degree, androstenedione, appear significant (Chart 1). It is a general belief that hirsutism (excess body hair) in the female and virilization (the masculinization of a female, with clitoral hypertrophy, excess muscle development, hair recession, and amenorrhea) are dose effects of androgen. As little as 2 mg per day of testosterone can virilize an adult woman.

Recent work by one of the authors has indicated that there is a pronounced rise in circulating androgen between prepuberty and puberty. The amount of androgen necessary to virilize a prepubertal girl is probably much less than that required for an adult.

Although historically the Zimmerman method for estimating urinary ketosteroids opened up the *in vivo* steroid field in the 1930's, it has taken a long time to put the ketosteroids and biologically active androgens into their proper place in medicine. The urinary and plasma 17-hydroxycorticoids or ketogenic steroids are measures of cortisol (hydrocortisone) metabolism and will not be discussed further.

The 17-ketosteroids in urine include a considerable number of steroids which possess a ketone group at the 17 position, allowing the formation of a blue-red color with dinitrobenzene. It is important to realize that all of these substances are metabolites of parent steroid hormones and that they possess little or no biological activity and are present in a conjugated, water-soluble form as glucuronosides or sulfates. A minor fraction (10 to 15 per cent) is made up of breakdown products of cortisol from the adrenal gland. The majority of these urinary metabolites in both sexes are

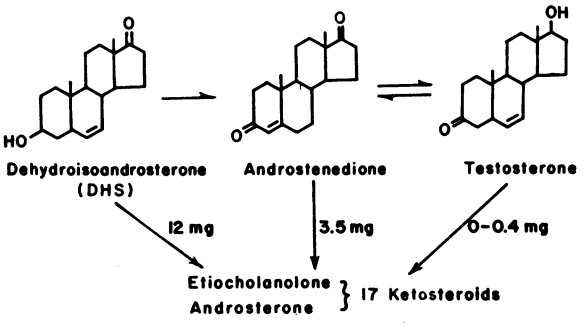


Chart 1.—The steroid precursors of the urinary C19-0_2 ketosteroids and production rates in normal females.

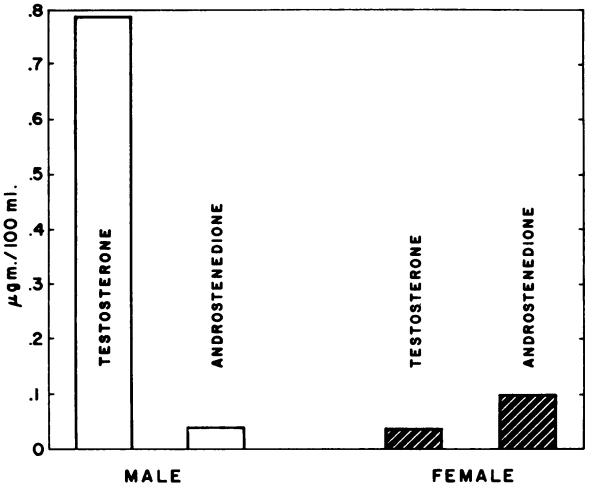


Chart 2.—Testosterone and androstenedione in human plasma.

derived from a steroid, dehydroisoandrosterone (Chart 1), and its sulfate. They have minor androgenicity and are secreted by the adrenal cortex in amounts equal to or exceeding the secretion of cortisol (15 to 25 mg a day).[8] Thus, the overwhelming majority of the urinary 17-ketosteroids are derived from the adrenal cortex and represent weakly androgenic substances. Nevertheless, as will be described later, the urinary 17-ketosteroid determination widely available to the practicing physician can be used to rule *in* certain disorders.

In recent years, the use of isotopes and chromatography for steroid assay has permitted accurate and sensitive measurement of hormones in biological fluids. Adult male and female urine contains 80 mcg and 8 mcg a day of testosterone glucuronoside respectively.[2] In blood, testosterone is present in a mean plasma concentration of 0.7 mcg per 100 ml in males but only 0.04 mcg per 100 ml in females (Chart 2).[6,9] The total daily production of testosterone which enters the circulation in a normal adult human is approximately 7 mg for males but only 0.4 mg for females. There appears to be a direct feedback to the pituitary, since luteinizing hormone (usually in the commercial form of chorionic gonadotropin) will increase plasma testosterone, while synthetic testosterone analogues will reduce endogenous testosterone secretion.[4,5]

In males, the system appears relatively simple in that the adult Leydig cell of the testes secretes essentially all the testosterone that enters the blood. The female—as we all know—is a much more complex creature. Although the story is not complete, the following will attempt to summarize the

current work. An adult female secretes, from the adrenal glands and the ovaries, about 3.5 mg a day of the weakly androgenic steroid androstenedione. This steroid is rapidly metabolized by the liver, as are most steroids. A glance at the chart of the structure of this steroid will indicate that it differs from the potent androgen testosterone only in the presence of a 17-ketone group instead of a 17-hydroxyl. This leads to the quip that a hydrogen ion is the only thing standing between a boy and a girl. Peripheral tissue has the capacity for making this interconversion. Most of this peripherally synthesized testosterone is conjugated, inactivated and excreted, but a fraction of it does enter the blood, where it provides about two-thirds of the total testosterone present in the plasma of females (Chart 3).[3]

Thus the possible source of excessive androgen in a female is:

- Increased secretion of testosterone by adrenal glands
- Increased secretion of testosterone by ovaries
- Increased secretion of androstenedione by adrenals
- Increased secretion of androstenedione by ovaries
- A combination of the above possibilities
- Abnormal conversion rates of androstenedione to testosterone

Since most of the testosterone synthesized in the liver does not enter the blood and circulate throughout the body as a biologically active hormone, the use of urinary testosterone metabolites in females gives very crude estimations of blood testosterone, and this approach should be interpreted with caution. In normal males the urinary approach does reflect circulating testosterone.

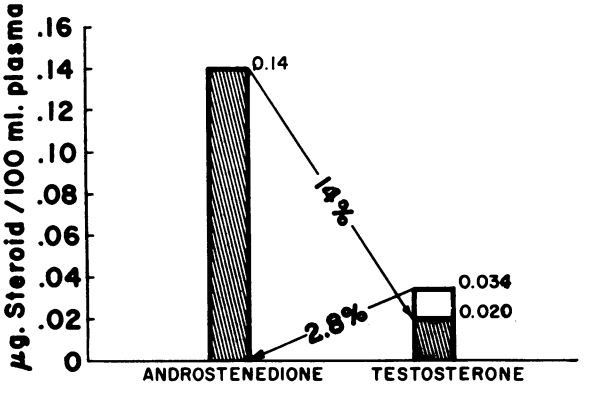
Virilizing disorders almost certainly indicate the presence of relatively large amounts of testosterone in blood. The clinical findings of virilization include most of the following: Deepening of the voice, severe acne, recession and balding of head hair, excessive facial and body hair, flushing of face and chest, amenorrhea, clitoral hypertrophy, sexual hyperactivity, increased muscle development and strength and changes toward a masculine habitus. The presence of a number of these findings warrants extensive clinical and laboratory diagnostic studies, since no better indicator of elevated testosterone could be obtained than this type of clinical bioassay.

The differential diagnosis of virilization includes various neoplastic or hyperplastic states of the adrenal cortex and ovary. Exogenous androgen or the various anabolic agents can mimic this process.

Cushing's disease, whether bilateral hyperplasia, adenoma or carcinoma, should be mentioned, although this is principally a problem of cortisol hypersecretion which involves signs and symptoms primarily of cortisol excess and can be diagnosed by the presence of elevated cortisol in plasma, lack of diurnal variation and increased urinary metabolites (17-hydroxycorticoids or ketogenics).

Congenital adrenal hyperplasia is a virilizing syndrome due to a biosynthetic defect in cortisol production which is overcome by increased stimulation of pituitary ACTH, but at the price of heightened secretion of dehydroisoandrosterone, androstenedione and other steroid precursors. As a result, in patients with this condition the ketosteroids are higher than in other persons of the same age group, and there is increased androstenedione and testosterone in the blood. In urine, both the 17-ketosteroids and pregnanetriol are increased. A physiological dose of glucocorticoid such as prednisone 2.5 mg three times a day or dexamethasone 0.5 mg twice a day will suppress the ketosteroids and pregnanetriol and serve as both diagnostic test and long-term therapy.

Rarely, an adenoma or carcinoma of the adrenal cortex will be present and lead to production of biologically active androgens. In this neoplastic disorder of the adrenal cortex, there is considerable disorganization of steroid biosynthesis, leading to production of large amounts of dehydroiso-



FEMALE PERIPHERAL BLOOD

Chart 3.—The contribution of androstenedione to plasma testosterone in females. The hatched areas represent androstenedione secretion and contributions. The arrows represent the rates of conversion. The clear area represents secreted testosterone.

androsterone and its sulfate. Hence the urinary 17-ketosteroids are almost always strikingly elevated, typically to between 40 and 150 mg a day (normal 5 to 15 mg). As is generally true of a neoplasm, no central nervous system pituitary control of secretion rate is apparent and even large doses of a cortisone analogue such as dexamethasone (2 mg four times a day) will not suppress the elevated ketosteroids.

The ovary may be the site of the abnormal androgen secretion. The Stein-Leventhal or polycystic ovary syndrome is a rather variable disorder whose essence is menstrual abnormalities, relative infertility and usually hirsutism with only occasional and mild degrees of virilization. The polycystic ovary and perhaps the adrenal glands secrete moderate amounts of testosterone and androstenedione. Since the ovary is the primary site of disease, minimal increases in dehydroisoandrosterone secretion are present and the urinary 17-ketosteroids are normal or only slightly elevated. The diagnosis can be made by the overall picture. Ovarian sclerocystosis, usually with enlargement, can be determined by careful pelvic examination or culdoscopy.

Prednisone in low dosage (5.0 to 7.5 mg a day in divided doses) has been effective in the majority of cases, especially in fertility control. Clomiphene (50 mg twice a day) for five to seven days, perhaps by altering the ratio of secreted pituitary gonadotropin, causes ovulation in up to 75 per cent of patients, and conception occurs in approximately half of them. Wedge resection, an unknown stimulus, is less often utilized at the present time as a therapeutic approach.

Again as in the adrenal glands there are very rare masculinizing tumors which carry a plethora of names based upon histological appearance (arrhenoblastoma, luteoma, thecoma, among others) although endocrinologically they behave similarly. These tumors secrete a potent androgen, probably testosterone. The ketosteroids are normal or low. A significant number of these masculinizing ovarian tumors are not palpable by the bimanual examination. However, the presence of frank virilization should lead to complete diagnostic studies, including exploratory laparotomy if necessary. To recapitulate, the presence of normal or low urinary 17-ketosteroids implicates the ovary. The masculinizing ovarian tumor is rare. Perhaps one or two a year are seen at major university centers. Very rarely an undifferentiated carcinoma or adrenal rest of the ovary will also secrete dehydroisoandrosterone, elevate the urinary 17-ketosteroids and resist suppression with cortisol analogues.

A recurrent theme in this discussion is the use of the urinary 17-ketosteroid assay. Although not a representation of androgen level, the ketosteroids can be used to implicate and rule in adrenal disease. The suppression with exogenous steroid generally differentiates between hyperplasia and autonomous adrenal tumor. The finding of normal or low urinary ketosteroid suggests an ovarian source (Chart 4).

This brings us to the major entity, at least in terms of the physicians' experience. Perhaps 90 per cent of all cases of hirsutism are "idiopathic" or simple hirsutism. Patients with simple hirsutism, whether obese or of normal body build, have varying degrees of increased facial and body hair and frequently mild acne and oily skin. No other signs or symptoms of virilization are present. A few patients have menstrual abnormalities, but associated psychological factors are usually involved. Most endocrinologists, especially those active in this particular field, feel that these patients represent a diverse group of mild disorders. This includes hereditary influences, obesity with some hypothalamic abnormality, local factors bearing on the hair follicle and perhaps mild abnormalities in androgen secretion or peripheral metabolism. A minor group have slightly elevated urinary ketosteroids, but otherwise normal adrenal function. The entire group suppress normally (>50 per cent) with small doses of a cortisol analogue administered for one week.

The major point here is to recognize the most common syndrome in the androgen area. An adequate investigation should include a careful pelvic

Chart 4.—Female Androgens.

URINARY METABOLITES

(a) *Urinary androsterone and 5β-androsterone* arise mainly from androstenedione produced from dehydroisoandrosterone. This androstenedione is poorly converted to testosterone in the liver and even less to testosterone in the blood.

(b) *Urinary testosterone glucuronide* arises mainly from secreted androstenedione. This testosterone is poorly transferred to testosterone in the blood.

BLOOD TESTOSTERONE

(c) *Sixty per cent blood testosterone* arises mainly from secreted androstenedione. This testosterone may be produced extrahepatically or in the liver.

(d) *The remaining 40 per cent of the blood testosterone* may be secreted, or produced in the liver from dehydroisoandrosterone, or both. It is most likely to be secreted testosterone.

examination, the exclusion of virilizing signs and the presence of normal urinary 17-ketosteroids (or suppressibility if slightly elevated to 50 per cent of initial value).

Even though the disorder is not completely understood at this time, making a positive diagnosis is important. Some endocrinologists have suggested long-term steroid suppression. The authors are not convinced of the efficacy of this approach. Only occasionally will hair growth be significantly reduced by this means. Reliance must be placed at this time on electrolysis and reassurance to the patient that this is not a serious disorder. The facial hair can be removed and controlled. On the research horizon is the possibility of using antiandrogens,[1] or other drugs.

No mention has been made of the use of a plasma testosterone estimation. This determination is available in a number of research laboratories in this country (including the authors') and also available in a few specialized commercial laboratories. The authors feel at this time that this procedure remains a research tool. In the near future, in selected cases of virilization a practical approach may be to study the effect of corticotropin or gonadotropin on plasma testosterone and androstenedione to determine the site and responsiveness to appropriate stimuli. The presence of virilization unquestionably indicates elevated testosterone. Simple hirsutism may or may not be associated with elevated testosterone levels. What appears to count are the clinical indications as noted above for an aggressive approach including culdoscopy or laparotomy. This attitude has been reached as a result of both clinical and research experience.[7,10]

However, it is certainly helpful to have further documentation and quantitation. The major point of this paper is to correlate the research findings with the everyday clinical problem and to point out that proper diagnosis can almost always be made with the widely available tools that an informed physician and a typical clinical laboratory can effectively use.

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